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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,072	08/30/2001	David R. Lindsay	LIDR5001JP	8673

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EXAMINER	
SHEIKH, HUMERA N	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 08/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,072	LINDSAY, DAVID R.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 10-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the request for extension of time (3 months-granted), the Request for Continued Examination (RCE) under 37 C.F.R. §1.114 and Applicant's Arguments/Response, all filed 04/28/04 is acknowledged.

Claims 1-8 and 10-20 are pending. Claims 1, 10 and 11 have previously been amended. Claim 9 has been cancelled. Claims 1-8 and 10-20 are rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-8 and 10-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Oshlack *et al.* (US Pat. No. 6,696,088 B2).

Oshlack *et al.* disclose tamper-resistant, controlled release oral opioid agonist formulations comprising (i) an opioid agonist present in releasable form and (ii) a sequestered opioid antagonist that is present in a substantially non-releasable form

when the dosage form is administered intact, but becomes bioavailable when the dosage form is tampered with by chewing, crushing, grinding or shearing. A method for preventing abuse of an oral opioid dosage form that includes a dose of opioid antagonist, which is sequestered (not bioavailable when dosage form is intact but is bioavailable when dosage form is tampered with) is also disclosed.

According to Oshlack *et al.*, when the dosage form is tampered with, the integrity of the substantially non-releasable form of opioid antagonist will be compromised, and the opioid antagonist will be made available to be released. Because the opioid antagonist is present in a substantially non-releasable form, it does not substantially block the analgesic effect of the opioid agonist when the dosage form is orally administered intact, and does not pose a risk of precipitation of withdrawal in opioid tolerant or opioid-dependent patients. The opioid antagonist, which is in substantially non-releasable form, can be in the form of multiparticulates or particles that are individually coated with a material that substantially prevents release of the antagonist. When the antagonist is in the form of multiparticulates coated with a sequestering material, the multiparticulates can also be in the form of inert beads coated with the antagonist and overcoated with the material or alternatively in the form of a granulation comprising the antagonist and the material. The coating is impermeable to the opioid antagonist contained therein and is insoluble in the gastrointestinal system, thus substantially preventing release of the opioid antagonist (see reference column 3, lines 52-58); (col. 4, lines 4-17); (col. 5, lines 54-59); (col. 6, lines 25-31); (col. 8, line 44 – col. 9, line 40); Abstract, Examples and Claims.

Opioid *agonists* disclosed include morphine, hydromorphone, hydrocodone, oxycodone, codeine, levorphanol, meperidine, methadone and mixtures thereof (col. 10, lines 3-6); (col. 14, line 21- col. 15, line 10).

Opioid *antagonists* disclosed include naltrexone, naloxone, nalmefene, cyclazacine, levallorphan, pharmaceutically acceptable salts and mixtures thereof (col. 10, lines 7-10).

The opioid dosage composition is formulated in sustained and controlled release tablets and capsule dosage forms (col. 10, lines 41-58). Pellets, beads and the like are disclosed at column 6, lines 32-41.

The opioid antagonists are coated with hydrophobic or hydrophilic materials, whereby suitable hydrophobic materials include natural and synthetic waxes, hydrocarbons, normal waxes, fatty acids, celluloses, acrylic polymers and the like and mixtures thereof. A combination of two or more hydrophobic materials can also be included. If an additional hydrophobic material is included, it is preferably selected from natural and synthetic waxes (col. 27, line 42 – col. 28, line 53); (col. 23, lines 14-26).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8 and 10-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palermo et al. (US Pat. No. 6,228,863 B1) in view of Oshlack *et al.* (US Pat. No. 6,696,088 B2).

Palermo *et al.* teach a controlled release oral dosage pharmaceutical formulation comprising: an analgesically effective amount of an orally active opioid agonist together with an opioid antagonist into an oral dosage form, wherein the amount of antagonist being sufficient to counteract the effects of the opioid agonist/antagonist combination to provide an aversive effect in a physically dependent human subject when the dosage is orally administered. A method of reducing the abuse potential of an oral dosage form of an opioid analgesic, which comprises combining an analgesically effective amount of an opioid agonist together with an opioid antagonist is also taught (see reference column 4, line 36 through column 6, line 35); and claims.

Opioid *agonists* include hydrocodone, hydromorphone, oxycodone, morphine sulfate, meperidine, codeine, methadone, or salts thereof, or mixtures thereof (col. 10, lines 8-15); and claims.

Opioid *antagonists* include naltrexone, naloxone, nalmephene, cyclazocine and levallorphan (col. 8, lines 26-35).

Oral administration forms disclosed are tablets, capsules, liquids, powders or granules, microparticles, drops, lozenges, caplets, gelcaps and the like, for example (col. 6, lines 40-45); (col. 12, lines 45-50).

Palermo et al. teach that the opioid dosage formulation is a sustained release formulation comprising a sustained release coating of a matrix containing the opioid agonist and opioid antagonist, where the sustained release coating contains at least a portion of the sustained release carrier in the dosage form. It is preferred that the sustained release preparation be prepared in a manner that the opioid agonist and the opioid antagonist are combined in a matrix or interdispersed so as to force an addict to utilize extraction methodology to separate these drugs (col. 5, line 64 – col. 6, line 9).

Palermo *et al.* do not teach explicitly teach a separate coating for the opioid antagonist.

Oshlack *et al.* ('088) teach tamper-resistant, controlled release oral opioid agonist formulations comprising (i) an opioid agonist present in releasable form and (ii) a sequestered opioid antagonist that is present in a substantially non-releasable form when the dosage form is administered intact, but becomes bioavailable when the dosage form is tampered with by chewing, crushing, grinding or shearing. The opioid antagonist particles are individually coated with a material that substantially prevents

release of the antagonist. The coating is impermeable to the opioid antagonist contained therein and is insoluble in the gastrointestinal system, thus substantially preventing release of the opioid antagonist (see reference column 3, lines 52-58); (col. 4, lines 4-17); (col. 5, lines 54-59); (col. 6, lines 25-31); (col. 8, line 44 – col. 9, line 40); Abstract, Examples and Claims.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the combined teachings of Oshlack *et al.* within Palermo *et al.* to provide for a separately coated opioid antagonist formulation because Oshlack *et al.* teach an opioid agonist/antagonist formulation, wherein the opioid antagonist is distinctly coated to provide a sequestered antagonist formulation whereby the coating is impermeable to the opioid antagonist contained therein and is insoluble in the gastrointestinal system with the expectation of obtaining an opioid agonist/antagonist formulation in which the release of release of the opioid antagonist is substantially prevented until the antagonist dosage is tampered with (i.e., by crushing, chewing), as similarly desired by Applicant.

Claims 1-8 and 10-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaiko *et al.* (US Pat. No. 6,277,384 B1) in view of Oshlack *et al.* (US Pat. No. 6,696,088 B2).

Kaiko *et al.* teach a controlled release oral dosage formulation comprising a combination of an orally analgesically effective amount of an opioid agonist and an

orally active opioid antagonist in an amount which does not cause a reduction in the level of analgesia elicited from the dosage upon oral administration to a non-therapeutic level and which provides a mildly negative aversive experience in physically dependent human subjects. A method of preventing oral abuse of an oral opioid formulation by combining an opioid agonist together with an opioid antagonist is also disclosed (see reference column 4, line 46 through column 7, line 42); and claims.

Opioid *agonists* include hydrocodone, hydromorphone, oxymorphone, morphine, meperidine, salts and mixtures of any of the foregoing (col. 11, lines 34-57).

Opioid *antagonists* include nalxone, naltrexone, nalmephene, cyclazocine (col. 10, lines 3-12).

Oral administration forms disclosed are tablets, capsules, liquids, powders or granules, microparticles, drops, lozenges, caplets, gelcaps, inert beads and the like (col. 7, lines 17-27).

Kaiko *et al.* teach that the dosage forms provide a sustained release of the opioid antagonist whereby part or all of the opioid antagonist can be in sustained release form, carried out via a sustained release coating of a matrix containing the opioid agonist and opioid antagonist (col. 7, lines 28-42).

Kaiko *et al.* do not teach explicitly teach a separate coating for the opioid antagonist.

Oshlack *et al.* ('088) teach tamper-resistant, controlled release oral opioid agonist formulations comprising (i) an opioid agonist present in releasable form and (ii)

a sequestered opioid antagonist that is present in a substantially non-releasable form when the dosage form is administered intact, but becomes bioavailable when the dosage form is tampered with by chewing, crushing, grinding or shearing. The opioid antagonist particles are individually coated with a material that substantially prevents release of the antagonist. The coating is impermeable to the opioid antagonist contained therein and is insoluble in the gastrointestinal system, thus substantially preventing release of the opioid antagonist (see reference column 3, lines 52-58); (col. 4, lines 4-17); (col. 5, lines 54-59); (col. 6, lines 25-31); (col. 8, line 44 – col. 9, line 40); Abstract, Examples and Claims.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the combined teachings of Oshlack *et al.* within Kaiko *et al.* to provide for a separately coated opioid antagonist formulation because Oshlack *et al.* teach an opioid agonist/antagonist formulation, wherein the opioid antagonist is distinctly coated to provide a sequestered antagonist formulation whereby the coating is impermeable to the opioid antagonist contained therein and is insoluble in the gastrointestinal system with the expectation of obtaining an opioid agonist/antagonist formulation in which the release of release of the opioid antagonist is substantially prevented until the antagonist dosage is tampered with (i.e., by crushing, chewing), as similarly desired by Applicant.

Response to Arguments

Applicant's arguments filed 04/28/04 have been fully considered but they are not persuasive.

Applicant specifically argued, "The elements of claim 9 were incorporated into independent claims 1 and 11 to more specifically identify the separate coating of the antagonist. The coating of the antagonist is further characterized by two qualities.

The coating: 'will not release a sufficient quantity of said antagonist to counteract the effects of the pharmaceutical composition when taken orally' and the coating: 'will not release said sufficient amount if it is chewed or crushed before oral administration.'

These two qualities of the coating of the antagonist distinguish it from the type of form of the pharmaceutical composition, which is a "controlled release dosage form". Controlled release is described as being a release of a dose over time by either a semi-permeable membrane or other encapsulation with varying levels of a diffusion barrier. In contrast, the coating of the antagoinist is claimed to be of a substance that does not release a "dose" at all. The coating will not release a sufficient quantity of antagonist to counteract the effects of the pharmaceutical composition."

These arguments have been thoroughly considered, but were not found persuasive. The instant claims have now been rejected as follows:

Claims 1-8 and 10-20 are rejected under 35 U.S.C. 102(e) as being anticipated by Oshlack et al. (US Pat. No. 6,696,088 B2).

Oshlack *et al.* disclose tamper-resistant, controlled release oral opioid agonist formulations comprising (i) an opioid agonist present in releasable form and (ii) a sequestered opioid antagonist that is present in a substantially non-releasable form when the dosage form is administered intact, but becomes bioavailable when the dosage form is tampered with by chewing, crushing, grinding or shearing.

Claims 1-8 and 10-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Palermo et al. (US Pat. No. 6,228,863 B1) in view of Oshlack et al. (US Pat. No. 6,696,088 B2).

The teachings of Palermo *et al.* have been delineated above. Palermo *et al.* do not teach explicitly teach a separate coating for the opioid antagonist. Oshlack *et al.* is relied upon to resolve this only deficiency of Kaiko et al. by teaching an opioid agonist/antagonist formulation wherein the opioid antagonist is separately coated with a material that substantially prevents release of the antagonist. The coating is impermeable to the opioid antagonist contained therein and is insoluble in the gastrointestinal system, thus substantially preventing release of the opioid antagonist. Because the opioid antagonist is present in a substantially non-releasable form, it does not substantially block the analgesic effect of the opioid agonist when the dosage form is orally administered intact, and does not pose a risk of precipitation of withdrawal in opioid tolerant or opioid-dependent patients.

Claims 1-8 and 10-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaiko et al. (US Pat. No. 6,277,384 B1) in view of Oshlack et al. (US Pat. No. 6,696,088 B2).

The teachings of Kaiko *et al.* have been discussed above. Kaiko *et al.* are lacking only in the sense that they do not teach explicitly teach a separate coating for the opioid antagonist. Oshlack et al. is relied upon to resolve this only deficiency of Kaiko et al. by teaching an opioid agonist/antagonist formulation wherein the opioid antagonist is separately coated with a material that substantially prevents release of the

antagonist. The coating is impermeable to the opioid antagonist contained therein and is insoluble in the gastrointestinal system, thus substantially preventing release of the opioid antagonist. Because the opioid antagonist is present in a substantially non-releasable form, it does not substantially block the analgesic effect of the opioid agonist when the dosage form is orally administered intact, and does not pose a risk of precipitation of withdrawal in opioid tolerant or opioid-dependent patients.

In summary, the prior art teaches and recognizes opioid agonist/antagonist formulations that utilize a separate, distinct coating for the opioid antagonist, in order to provide for a controlled, sequestered release dosage formulation of the opioid antagonist. The opioid antagonists are in sequestered forms, so as to provide for a dosage form wherein the antagonist is substantially non-releasable and the dosage form is not bioavailable when intact but becomes bioavailable when dosage form is tampered with, such as by crushing, chewing, grinding or shearing. There is no significant distinction observed between the instant invention and the prior art since the prior art clearly discloses, teaches and suggests opioid antagonist formulations whereby the antagonists are coated so as to not release a substantial amount or no amount at all of the antagonist, in order that the effects of the pharmaceutical composition (agonist) are not counteracted. The prior art teaches the utilization of similar components for the same field of endeavor and to solve the same problems as that desired by Applicants. Hence, the instant invention is fully anticipated and is rendered *prima facie* obvious over the cited prior art of record.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday through Friday from 8:00A.M. to 5:30P.M., alternate Fridays from 8:00 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page, can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

hns
July 26, 2004

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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